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Relations Between Subclinical Disease Markers and Type 2 Diabetes, Metabolic Syndrome, and Incident Cardiovascular Disease: The Jackson Heart Study

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OBJECTIVE

The presence of subclinical disease measures has been directly associated with the development of cardiovascular disease (CVD) in whites. African Americans (AAs) in the U.S. are at higher risk of CVD compared with non-Hispanic whites; however, data on the prevalence of subclinical disease measures in AAs and their association to CVD remain unclear and may explain the higher CVD risk in this group.

RESEARCH DESIGN AND METHODS

We evaluated 4,416 participants attending the first examination of the Jackson Heart Study (mean age 54 years; 64% women) with available subclinical disease measures.

RESULTS

There were 1,155 participants (26%) with subclinical disease, defined as the presence of one or more of the following: peripheral arterial disease, left ventricular hypertrophy, microalbuminuria, high coronary artery calcium (CAC) score, and low left ventricular ejection fraction. In cross-sectional analyses using multivariable-adjusted logistic regression, participants with metabolic syndrome (MetS) or diabetes (DM) had higher odds of subclinical disease compared with those without MetS and DM (odds ratios 1.55 [95% CI 1.30–1.85] and 2.86 [95% CI 2.32–3.53], respectively). Furthermore, the presence of a high CAC score and left ventricular hypertrophy were directly associated with the incidence of CVD (265 events) in multivariable-adjusted Cox proportional hazards regression models ($P < 0.05$). In prospective analyses, having MetS or DM significantly increased the hazard of incident CVD, independent of the presence of subclinical disease ($P < 0.001$).

CONCLUSIONS

In our community-based sample of AAs, we observed a moderately high prevalence of subclinical disease, which in turn translated into a greater risk of CVD, especially in people with MetS and DM.

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African Americans (AAs) in the U.S. are at a higher risk of cardiovascular disease (CVD) compared with non-Hispanic whites (1). They also have the highest prevalence of hypertension, type 2 diabetes (DM), and obesity compared with other ethnicities worldwide, and AA women have a greater burden of metabolic syndrome (MetS) (1). In addition, studies (of predominantly white samples) have suggested that the presence of subclinical disease is directly associated with the development of overt CVD (2,3). These observations raise the possibility that a higher burden of subclinical disease in AAs (especially in those with MetS and DM) may contribute directly to the greater burden of CVD in this group. Interestingly, despite the higher burden of select risk factors and CVD among AAs compared with whites, data on the prevalence of subclinical disease measures are more varied. For instance, the prevalence of coronary artery calcium (CAC) is lower in AAs (4–6), whereas they have the highest carotid intima-media thickness compared with other ethnicities (1). In addition, the incidence and progression of CAC is greater in whites compared with AAs (5). The exact reasons for these ethnic differences in the prevalence and incidence of CAC are not well understood and are not explained by the burden of standard risk factors (4,7,8). Yet, in terms of prognostic significance, CAC (when present) is associated with a greater mortality hazard in AAs compared with whites (9). These observations raise the question of whether a higher burden of subclinical disease in AAs may contribute to a greater risk of CVD compared with whites. Therefore, comprehensively assessing the prevalence of subclinical disease among AAs and evaluating its relation to the incidence of CVD in this group are critical.

MetS and DM are two conditions that have been associated with a greater prevalence of subclinical CVD (2). This is not surprising because the MetS is a combination of risk factors and DM itself is a powerful atherogenic influence. Investigators also have reported that the presence of DM is more strongly associated with progression of subclinical atherosclerosis in AAs compared with whites (5). In this context assessing whether the presence of MetS and DM promotes the development of subclinical disease in AAs, which in turn enhances the development of overt CVD, is of interest. Accordingly, we assessed the prevalence of subclinical disease among AAs (with and without MetS and DM) and hypothesized that the presence of subclinical disease greatly increases the propensity for overt CVD in this group.

RESEARCH DESIGN AND METHODS

Study Population and Covariate Definition

The design and recruitment methods for the Jackson Heart Study (JHS) cohort have been previously described (10). A total of 5,301 AAs were recruited between 2000 and 2004 from Jackson, MS, and the surrounding tri-county area (Hinds, Rankin, and Madison Counties) and attended the first examination cycle. A total of 885 participants were excluded from the analysis in this investigation, specifically participants with prevalent CVD at baseline (n = 558), participants without information on MetS and/or DM (n = 272), and those without information on subclinical disease measures (defined as peripheral arterial disease [PAD], left ventricular [LV] hypertrophy, microalbuminuria, high CAC, and low LV ejection fraction) (n = 55). After these exclusions, 4,416 participants were eligible for our investigation.

Participants were defined as having DM if they had a fasting glucose $\geq$126 mg/dL or if they were taking insulin or oral hypoglycemic medications. MetS was defined by the presence of three or more of the following five metabolic derangements: *1*) waist circumference $\geq$88 cm for women and $\geq$102 cm for men; *2*) HDL $<$40 mg/dL for men and $<$50 mg/dL for women; *3*) fasting triglycerides $\geq$150 mg/dL or the use of lipid-lowering therapy; *4*) systolic blood pressure (BP) $\geq$130 mmHg or diastolic BP $\geq$85 mmHg or the use of hypertension medications; and *5*) a fasting serum glucose $\geq$100 mg/dL or the use of medications for lowering blood glucose (impaired glucose homeostasis) (11).

Subclinical Disease

Five subclinical disease phenotypes were measured for this study (Supplementary Table 1). CAC was measured with contrast tomographic angiography using a 16-channel multidetector with cardiac gating (LightSpeed Pro16; GE Healthcare, Milwaukee, WI). The core reading center where both image analysis and quality control were performed was located at Wake Forest University School of Medicine in Winston-Salem, NC. Calcified arterial plaques were computed using a TeraRecon Aquarius Workstation (TeraRecon, San Mateo, CA). Coronary calcium was scored in Hounsfield units. The presence of CAC was defined as having an Agatston score $>$10 (12,13). It should be noted that CAC was not measured during the same examination cycle as the other subclinical disease measures evaluated in this investigation; therefore we "carried back" the values for this variable from a later examination (4 years apart).

To determine ankle-brachial index (ABI)-defined PAD, two systolic BP measurements were taken at the ankle on each lower extremity while the participant was in the supine position. The brachial systolic BP, usually using the right brachial artery, was also measured twice. Two ABIs (one for the right and one for the left) were calculated as the average of the two ankles' systolic BP measurements divided by the average of the two brachial readings. The lower of the two ABIs was considered the ABI for the participant for the current investigation. To exclude falsely high ABIs resulting from arterial incompressibility, ankle systolic BP values that were 75 mmHg above the brachial systolic BP were excluded. Participants were considered to have ABI-defined PAD if the ABI was $<$0.9 (2).

Two-dimensional and M-mode echocardiography was performed using a Sonos 4500 cardiac ultrasound machine (Hewlitt Packard, Andover, MA). Measurements were performed offline by a trained echocardiographer (T.E.S.) based on American Society of Echocardiography recommendations (14). LV mass was measured in M-mode and was calculated using the American Society of Echocardiography–corrected formula: LV mass (g) = 0.8×1.04 [(LV end diastolic diameter + IVST + PWT)^3 – (LV end diastolic diameter)^3] + 0.6, where IVST is the interventricular septal wall thickness and PWT is the posterior wall thickness. LV ejection fraction was determined visually. Quality control was performed by local (T.E.S.) and outside (P.R.L.) expert readers. For this analysis, LV hypertrophy was defined as an LV mass indexed to height$^{2.7}$ $>$51 g/ht (3,15,16), and a low ejection fraction was defined as an LV ejection fraction $<$50%.

Finally, urinary albumin was measured using kit reagents and the ProSpec nephelometric analyzer (Dade Behring GMBH, Marburg, Germany). The interassay coefficient of variation was 3.2%. For the current analysis, microalbuminuria was defined as an albumin-to-creatinine ratio>25 μg/mg in men and >35 μg/mg in women (2).

The prevalence of any subclinical disease was defined by the presence of at least one component of the five subclinical disease phenotypes indicating abnormality. However, we excluded the participants who had more than three missing values among all five phenotypes and had normal values for the remaining components. In addition, those who had three or fewer missing components and normal values for the remaining components were considered as not having subclinical disease. We also compared the prevalence of subclinical disease between those who had available all subclinical disease components and the components used in the current investigation (prevalence of subclinical disease was 26% and 27%, respectively), which was not significantly different (P = 0.358). We did not attempt to relate individual components of subclinical disease to the incidence of CVD because these have been reported in previous studies.

Follow-up and CVD Events

To determine the occurrence of all CVD events, all participants were followed from the first examination until 31 December 2010 through periodic examinations at the JHS and a review of hospital and physician office visit records. All CVD events included ischemic stroke, angina, myocardial infarction (MI), intermittent claudication, congestive heart failure (CHF), stroke death, and other CVD death. More specifically, ischemic stroke was defined based on ICD-9 code 435 and ICD-10 code G45 (17). Angina was defined by the presence of chest pain or discomfort. MI was defined by a combination of the presence of cardiac pain, a change in enzymes, and electrocardiographic findings (17). Hospitalized MI was defined using ICD-9 codes 402, 410–414, 427, 428, and 518.4. CHF was defined using *1*) a discharge diagnosis of ICD-9 code 428 and/or underlying cause of death (code I50); and *2*) radiographic findings consistent with CHF or increased venous pressure >16 mmHG or dilated ventricle/LV ejection fraction <40% on echocardiography/multigated acquisition scan/MRI scan; or *3*) autopsy finding of pulmonary edema/CHF (17). Death was confirmed using death certificates; questionnaires completed by physicians, coroners, or medical examiners; and interviews with the next of kin. The criteria for classifying death from coronary heart disease (CHD) are based on any combination of *1*) chest pain; *2*) history of MI, CHD, or angina; *3*) the absence of evidence of other probable cause of death; and/or *4*) the use of ICD-9 codes (i.e., 250, 401, 402, 410–414, 427–429, 440, 518.4, 798, 799) or ICD-10 codes (E10–14, I10–11, I21–25, I46–51, I70, I97, J81, J96, R96, R98–99) to identify deaths from CHD (17). The outcome for this study was the first incidence of any CVD event.

Statistical Methods

Descriptive statistics (mean ± SD or percentages) were computed for demographic and clinical characteristics for three mutually exclusive groups: those with DM (DM group), those with MetS but no DM (MetS group), and those with neither DM nor MetS (referent group). Because the distributions of the CAC score and LV mass index were skewed, the geometric means and SDs of these variables are reported.

Multivariable logistic regression models were estimated to determine the relations between the prevalence of each component of subclinical disease (dependent variable) and the prevalence of MetS and DM (independent variable), adjusting for age, sex, smoking, LDL, education, and percent of dietary fat. We did not use BP, HDL, blood glucose, or other variables that may be along the causal pathway as adjustment variables because several of these risk factors are used to define MetS. Odds ratios (ORs) and their respective 95% CIs were calculated separately for participants with MetS and DM and those with either MetS or DM. We also compared the ORs for each component between the MetS and DM groups.

Multivariable Cox proportional hazards regression models were estimated for each group separately (MetS, DM, and referent) to evaluate the association between the hazard of new-onset CVD and the prevalence of each component of subclinical disease (as defined above). All assumptions for proportionality of hazards were met. We did not, however, evaluate microalbuminuria and low ejection fraction in this part of the analyses because of the small number of incident CVD events among participants presenting with these components. To examine the risk of CVD associated with MetS, DM, and subclinical disease—and to evaluate the impact of subclinical disease with MetS and DM on the hazard of the CVD event—we also used Cox proportional hazards regression models, adjusting for age, sex, smoking, LDL, education, and percent of dietary fat. Furthermore, we evaluated the interactions between the presence of subclinical disease and MetS and DM. Finally, we compared the hazard ratios (HRs) (with 95% CIs) for CVD for the components of subclinical disease between all three groups. We did not estimate receiver operating characteristic curves or assess the predictive utility of measurements because prediction was not the focus of this investigation. All analyses were conducted with SAS software version 9.2 (SAS Institute, Cary, NC). The study protocols were approved by the University of Mississippi Medical Center Institutional Review Board, and all participants provided written informed consent.

RESULTS

The baseline characteristics of our study sample are shown in Table 1. Individuals with the MetS had a higher prevalence of high CAC, LV hypertrophy, and microalbuminuria compared with the referent group ($P < 0.0001$ for all measures; Table 1). Participants with DM also had more components of the subclinical disease (such as PAD and microalbuminuria; Supplementary Table 1) compared with those in the referent group and those in the MetS group ($P < 0.05$ for all; Table 1). Approximately 42% of the participants had MetS or DM (17% had the latter), and 30% had impaired glucose homeostasis (n = 1,348 of the total study sample, which included 4,416 participants).

We evaluated the odds of having each individual component of subclinical disease among people with MetS and no DM, among those with DM but no MetS, and among those who did not have either DM or MetS (referent group). Adjusting for covariates, people with MetS had higher odds of having a high CAC score, LV hypertrophy, and microalbuminuria compared with the referent

Table 1—Clinical characteristics of the study population by metabolic status

Clinical characteristics*	Referent† (*n* = 2,553)	MetS (*n* = 1,102)	DM (*n* = 761)
Age, years	51.5 (13.04)	56.1 (11.8)	59.1 (10.46)
Male sex, %	38.82	31.22	30.88
High BP, %	53.04	92.47	88.82
BP, mmHg			
Systolic	123.2 (17.7)	130.9 (17.09)	130.8 (18.36)
Diastolic	78.6 (10.33)	81.3 (10.13)	77.2 (10.17)
Low HDL, %	20.36	71.69	41.55
HDL, mg/dL	55.5 (14.53)	44.4 (11.43)	50.7 (13.75)
Increased waist circumference, %	47.2	92.55	83.79
Waist circumference, cm	95 (15.08)	107.7 (13.99)	108.3 (15.47)
Impaired fasting glucose, %	5.17	41.42	100
Fasting blood glucose, mg/dL	88.4 (7.53)	96.7 (10.63)	149.7 (60.16)
High triglycerides, %	3.88	39.51	32.21
Triglycerides, mg/dL	83.77 (39.85)	141.08 (98.82)	134.32 (112.66)
Current smokers, %	12.61	12.48	9.89
PAD, %	4.66	5.45	9.27
ABI	1.14 (0.15)	1.16 (0.16)	1.13 (0.18)
High CAC score, %	14.04	25.51	40.64
CAC score	61.2 (5.82)	78.6 (6.51)	132 (6.08)
LV hypertrophy, %	4.13	8.82	13.68
LV mass index, g/m$^{2.7}$	32.9 (1.27)	37 (1.26)	38.7 (1.29)
Microalbuminuria, %	6.5	12.54	28.63
Low ejection fraction, %	2.07	2.25	2.97
Subclinical disease, %	18.99	29.94	44.65
Time to event, years	6.1 (1.07)	6.1 (1.27)	5.9 (1.6)

Average follow-up is 6 years. Data are a percentage or mean (SD). *Clinical characteristics are defined by the following criteria: high BP is defined as systolic BP ≥130 mmHg or diastolic BP ≥85 mmHg or use of antihypertensive medications; obesity is defined based on waist circumference: 102 cm (40 inches) in men, 88 cm (35 inches) in women; high triglycerides is defined as >150 mg/dL or currently taking a lipid-lowering medication; low HDL is defined as <40 mg/dL in men or <50 mg/dL in women; impaired fasting glucose is defined as a fasting glucose >100 mg/dL or medication use; PAD is defined as an ABI <0.9; high CAC score is defined as a raw CAC score >100; LV hypertrophy is defined as an LV mass index >51 g/m$^{2.7}$; low ejection fraction is defined as an ejection fraction <50%; microalbuminuria is defined as a urine albumin–to–creatinine ratio >25 μg/mg in men and >35 μg/mg in women. †The referent group is defined as those without DM or MetS. The CAC score and LV mass index are geometric means ± SDs. Subclinical disease is defined as the presence of any one of the following: PAD, high CAC score, LV hypertrophy, low ejection fraction, or microalbuminuria.

group (Table 2). Overall, people with MetS were at 1.5 times the odds of having at least one component of subclinical disease compared with the referent group. When comparing participants with DM with those in the referent group, data showed higher odds of all components of subclinical disease, as well as higher odds of having at least one component of subclinical disease in the former group, except for low ejection fraction (Table 2). In addition, those in the DM group had significantly higher odds of having at least one component of subclinical disease compared with those in the MetS group.

There were 265 CVD events in this sample (Table 3) during 6 years of follow-up. The incidence rates for CVD for the referent, MetS, and DM groups are shown in Table 3. Among the people belonging in the referent group (i.e., no MetS or DM), those who had a high CAC score had approximately four times the hazard of developing CVD compared with those who did not (Table 4). The same pattern was observed for people with at least one component of subclinical disease (Table 4). Among those with MetS, the same trend was observed when compared with the referent group, but only for the presence of high CAC score and LV hypertrophy, with approximately twice the hazard of CVD (Table 4). PAD did not show a significant association with the incidence of CVD in this group, perhaps because of a smaller number of CVD events. The presence of DM suggested a significant hazard of CVD for individuals having any component of the subclinical disease, with HRs ranging from 3.4 to 4.4. Overall, the presence of subclinical disease increased the hazard of developing CVD among all groups.

In addition, comparing the HRs among all groups, we observed a statistically significant difference in PAD between those with MetS and those with DM; more specifically, among those with PAD, people with DM are at a greater hazard of CVD compared with people with MetS.

Finally, we pooled all participants of our study sample to evaluate the association between the incidence of CVD and DM or MetS. We observed a strong association between the presence of MetS and the presence of DM with the incidence of CVD, with and without adjusting for the presence of subclinical disease. More specifically, those with MetS had approximately 1.8 and 2 times the hazard of CVD with and without adjustment for subclinical disease, respectively, and those with DM had 3.8 and 3.2 times the hazard of CVD with and without adjustment for subclinical disease, respectively (Table 5). When considering participants belonging to six different subgroups, the aforementioned associations retained their statistical significance as well as a similar strength of association (Table 5).

CONCLUSIONS

Principal Findings

This investigation provides a comprehensive assessment of the burden of subclinical disease in AAs in the community and elucidates the prognosis associated with presence of such disease. We used an extensive battery of tests to characterize the presence of subclinical disease in several vascular beds, including the presence of target organ damage. Our principal findings are threefold. First, about 42% of the participants had MetS or DM (17% had the latter), and 30% had impaired glucose homeostasis. Second, a substantial proportion of individuals (~25%) had evidence of subclinical disease. The prevalence of several subclinical disease measures was three- to fourfold higher in those with DM, and nearly twofold higher in those with MetS, compared with individuals without

Table 2—Odds of the components of the subclinical disease in the study population based on metabolic status

Components of subclinical disease*	Referent†	MetS			DM			
		OR	95% CI	*P* value	OR	95% CI	*P* value	*P* value‡
PAD	1	0.901	0.623–1.303	0.58	1.563	1.054–2.317	0.0261	0.045
High CAC score	1	1.734	1.327–2.265	<0.0001	4.348	3.176–5.953	<0.0001	<0.0001
LV hypertrophy	1	1.938	1.337–2.807	0.0005	3.041	2.008–4.606	<0.0001	0.112
Microalbuminuria§	1	1.947	1.429–2.652	<0.0001	4.794	3.43–6.701	<0.0001	<0.0001
Low ejection fraction	1	1.163	0.698–1.94	0.5621	1.366	0.746–2.504	0.3126	0.691
At least one component of subclinical disease	1	1.548	1.296–1.848	<0.0001	2.863	2.324–3.526	<0.0001	<0.0001

All models are adjusted for age, sex, smoking, LDL, education, and percent of fat. *Components of subclinical diseases are based on the following criteria: PAD is defined as an ABI <0.9; high CAC score is defined as a raw CAC score >100; LV hypertrophy is defined as an LV mass index >51 g/m$^{2.7}$; low ejection fraction is defined as an ejection fraction <50%; microalbuminuria is defined as a urine albumin–to–creatinine ratio >25 μg/mg in men and >35 μg/mg in women. †Referent group is defined as those without DM or MetS. ‡OR_{MetS} vs. OR_{DM}. §There were 49 participants assigned to the subclinical group based only on the presence of microalbuminuria.

these conditions. A high CAC score was the most frequent component of subclinical disease in our sample. Third, the presence of subclinical disease increased the incidence of CVD threefold overall, with HRs being substantially higher (four- to sevenfold) in individuals with MetS or DM. These findings (although observational) highlight the importance of detecting subclinical disease in AAs and aggressively managing those with presence of subclinical disease to lower the burden of CVD in this group.

Comparison With the Literature

Prevalence of Subclinical Disease in AAs

To our knowledge, no prior study has investigated the prevalence of subclinical disease in community-dwelling AAs using a panel of multiple measures, each individually associated with risk of CVD in prior reports. The high prevalence of DM in our sample is striking and likely contributes to the greater risk of CVD among AAs. The overall prevalence of subclinical disease was lower than that reported in middle-aged white participants in the Framingham Heart Study (FHS) in a previous report (2), although criteria for select measures (such as echocardiographic LV hypertrophy) differed in the two investigations. Although CAC was the most prevalent form of subclinical disease, the overall prevalence in our sample was much lower than that reported in the FHS, consistent with other prior observations in AAs (4,6–9,11). The presence of MetS or DM increased the odds of having subclinical disease 1.5- to 3-fold overall; the strength of the associations of these two conditions with subclinical disease measures was somewhat weaker than that from the FHS reported previously (two- to fourfold greater odds of subclinical disease).

Table 3—Incidence of CVD

Characteristics	Events (*n*)/patients at risk (*n*)	Person-years at risk (*n*)	Incidence rate per 1,000 person-years	Age- and sex-adjusted rate (95% CI)
Referent*				
All	79/2,553	15,543	5.08	2.64 (2.08–3.35)
No subclinical disease	31/2,018	12,378	2.50	1.1 (0.72–1.67)
Any subclinical disease present	43/473	2,776	15.49	4.04 (2.6–6.24)
MetS†				
All	78/1,102	6,690	11.66	5.28 (4.11–6.74)
No subclinical disease	36/751	4,609	7.81	4.75 (3.36–6.68)
Any subclinical disease present	37/321	1,915	19.32	8.25 (5.59–12.03)
DM				
All	108/761	4,477	24.12	9.62 (7.71–11.94)
No subclinical disease	41/409	2,480	16.53	10.44 (7.64–14.1)
Any subclinical disease present	61/330	1,870	32.62	17.07 (13.24–21.74)

*No MetS or DM; †No DM.

Prognosis of Subclinical Disease in AAs

The presence of a high CAC score (Agatston score >100) or echocardiographic LV hypertrophy increased the risk of incident CVD two- to fourfold. Despite a lower prevalence of subclinical disease measures in AAs in our sample (relative to the FHS), the strength of the association with incident CVD was stronger (HR 3.16 vs. 1.90 in FHS) (2). This observation is consistent with a previous report underscoring the greater mortality hazard among AAs (compared with whites) associated with CAC, despite a lower prevalence of CAC (9). Furthermore, in the presence of MetS and DM, the risk of CVD increased nearly five- to sevenfold; HRs for incident CVD associated with subclinical disease in these two conditions were somewhat lower among the FHS cohort.

Overall, our findings suggest that the presence of subclinical disease in AAs may contribute substantially to a greater burden of CVD in this group, consistent with our study hypothesis. Identifying AAs with DM and/or MetS and detecting the presence of subclinical disease in these subgroups and treating risk factors aggressively in these highest-risk individuals may be critical to prevent CVD in AAs.

Strengths and Limitations

The large community-based sample, the use of a comprehensive panel of tests assessing subclinical atherosclerosis

Table 4—Hazard of a cardiovascular event with prevalent subclinical diseases by metabolic status

	Referent* (79/2,553[a])			MetS (78/1,102[a])			DM (108/761[a])		
	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value
PAD†	1.90	0.92–3.94	0.084	1.38	0.61–3.13	0.438	4.36	2.20–8.64	<0.0001
High CAC score‡	4.32	1.97– 9.49	<0.0001	2.17	1.06–4.42	0.033	3.41	1.35–8.65	0.010
LV hypertrophy§	4.75	2.24–10.07	<0.0001	2.56	1.20–5.45	0.015	4.40	2.18–8.87	<0.0001
At least one component	3.49	2.13–5.73	<0.001	1.63	0.99–2.68	0.056	1.64	0.99–2.75	0.057

All models are adjusted for age, sex, smoking, LDL, education, and percent of fat. Pairwise comparisons between the groups were not statistically significant, except for the comparison of PAD between the MetS and the DM groups (1.38 vs. 4.36, respectively; $P = 0.04$). *The referent group is defined as those without DM or MetS; [a]number of CVD events over number of people at risk for the event; †PAD is defined as an ABI <0.9; ‡high CAC score is defined as a raw CAC score >100; §LV hypertrophy is defined as a LV mass index >51 g/m$^{2.7}$.

and target organ damage, the routine nature of the evaluation of subclinical disease, and the combination of cross-sectional findings with a prospective study of the prognostic impact of subclinical disease strengthen our investigation. Furthermore, we were able to relate both individual measures of subclinical disease and a composite measure to the incidence of CVD. However, several limitations must be acknowledged. Our sample was middle-aged and of AA descent, limiting the generalizability of our results to other age and ethnic groups. Also, AAs in the JHS, a cohort located in the Stroke Belt, may not be representative of AAs living elsewhere in the U.S. The estimates of the prevalence of subclinical disease may represent the upper bound of prevalence in AAs overall, given the high-risk nature of this sample; however, we submit that the large sample size provides for more accurate estimates. In addition, we excluded participants with missing subclinical disease measures, who typically tend to be sicker (e.g., older and with higher prevalence of hypertension, DM, and dyslipidemia) in an epidemiological context, which may bias our observed associations. CAC was not measured during the same examination cycle as the other subclinical disease measures evaluated in this investigation; therefore we "carried back" the values for this variable from a later examination (4 years apart). Limited data suggest that the prevalence of CAC remains stable over a short period of up to 5 years (CAC progression is typically 2%) (18), and because the interval between the two examination cycles was 4 years, we do think it is reasonable to "carry back" the CAC score without influencing the prospective findings of this investigation. However, caution should be exercised with regard to reference on the prevalence of subclinical disease. The small number of CVD events precludes the analysis of individual subcomponents of CVD, such as heart failure. For this same reason, we observe wide CIs for the HRs of the incidence of CVD. Finally, aiming for consistency and ease of comparison with our prior work on the same topic in whites in the FHS, heart failure was considered a form of CVD complication (2).

Table 5—Risk of cardiovascular event by metabolic status and presence of subclinical disease

	All CVD events (265/4,416)		
	HR	95% CI	*P* value
Model A (CVD risks associated with MetS and DM, not adjusting for subclinical disease)			
Referent group	Referent		
MetS*	2.02	1.45–2.80	<0.0001
DM	3.17	2.26–4.46	<0.0001
Model B† (CVD risks associated with MetS and DM, adjusting for presence/absence of subclinical disease)			
Referent group	Referent		
MetS	1.78	1.27–2.51	<0.0001
DM	3.79	2.52–5.69	<0.0001
Subclinical disease present	3.16	2.26–4.42	<0.0001
Model C (CVD risks associated with MetS and DM, by presence versus absence of subclinical disease)			
Referent group			
Subclinical disease absent	Referent		
Subclinical disease present	3.49	2.13–5.73	<0.0001
MetS			
Subclinical disease absent	2.64	1.607–4.35	0.0002
Subclinical disease present	4.48	2.68–7.49	<0.0001
DM			
Subclinical disease absent	4.36	2.56–7.45	<0.0001
Subclinical disease present	6.95	4.15–11.64	<0.0001

All models are adjusted for age, sex, smoking, LDL, education, and percent of fat. The referent groups are defined as those without DM or MetS. The interaction of subclinical disease and MetS and the interaction of subclinical disease and DM were significant ($P = 0.0175$ and $P = 0.038$, respectively). *No DM; †For model B, the referent group includes participants with neither MetS nor DM, but it may include participants with and without subclinical disease.

Conclusion

In our community-based sample of AAs we observed a moderately high prevalence of subclinical disease and target organ damage cross-sectionally, which in turn translated into a greater prospective risk of overt CVD, especially in people with MetS and DM. Overall, our findings are of public health importance because AAs have a disproportionately high burden of CVD in the U.S. relative to other racial groups (1). Accordingly, identifying and aggressively treating risk factors and assessing subclinical disease burden in

AAs may be important components of any approach directed at lowering the burden of CVD in this high-risk group.

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References

1. Go AS, Mozaffarian D, Roger VL, et al.; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics–2014 update: a report from the American Heart Association. Circulation 2014;129:e28–e292
2. Ingelsson E, Sullivan LM, Murabito JM, et al. Prevalence and prognostic impact of subclinical cardiovascular disease in individuals with the metabolic syndrome and diabetes. Diabetes 2007;56:1718–1726
3. Malik S, Budoff MJ, Katz R, et al. Impact of subclinical atherosclerosis on cardiovascular disease events in individuals with metabolic syndrome and diabetes: the Multi-Ethnic Study of Atherosclerosis. Diabetes Care 2011;34:2285–2290
4. Bild DE, Detrano R, Peterson D, et al. Ethnic differences in coronary calcification: the Multi-Ethnic Study of Atherosclerosis (MESA). Circulation 2005;111:1313–1320
5. Kronmal RA, McClelland RL, Detrano R, et al. Risk factors for the progression of coronary artery calcification in asymptomatic subjects: results from the Multi-Ethnic Study of Atherosclerosis (MESA). Circulation 2007;115:2722–2730
6. Orakzai SH, Orakzai RH, Nasir K, et al. Subclinical coronary atherosclerosis: racial profiling is necessary! Am Heart J 2006;152:819–827
7. Budoff MJ, Nasir K, Mao S, et al. Ethnic differences of the presence and severity of coronary atherosclerosis. Atherosclerosis 2006;187:343–350
8. Wagenknecht LE, Divers J, Bertoni AG, et al. Correlates of coronary artery calcified plaque in blacks and whites with type 2 diabetes. Ann Epidemiol 2011;21:34–41
9. Nasir K, Shaw LJ, Liu ST, et al. Ethnic differences in the prognostic value of coronary artery calcification for all-cause mortality. J Am Coll Cardiol 2007;50:953–960
10. Taylor HA Jr. The Jackson Heart Study: an overview. Ethn Dis 2005;15(Suppl. 6):S6-1-3
11. Grundy SM, Brewer HB Jr, Cleeman JI, Smith SC Jr, Lenfant C; American Heart Association; National Heart, Lung, and Blood Institute. Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. Circulation 2004;109:433–438
12. Hoffmann U, Brady TJ, Muller J. Cardiology patient page. Use of new imaging techniques to screen for coronary artery disease. Circulation 2003;108:e50–e53
13. Tullos BW, Sung JH, Lee JE, Criqui MH, Mitchell ME, Taylor HA. Ankle-brachial index (ABI), abdominal aortic calcification (AAC), and coronary artery calcification (CAC): the Jackson Heart Study. Int J Cardiovasc Imaging 2013;29:891–897
14. Devereux RB, Alonso DR, Lutas EM, et al. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. Am J Cardiol 1986;57:450–458
15. de Simone G, Devereux RB, Daniels SR, Koren MJ, Meyer RA, Laragh JH; de SG. Effect of growth on variability of left ventricular mass: assessment of allometric signals in adults and children and their capacity to predict cardiovascular risk. J Am Coll Cardiol 1995;25:1056–1062
16. Samdarshi TE, Taylor HA, Edwards DQ, et al. Distribution and determinants of Doppler-derived diastolic flow indices in African Americans: the Jackson Heart Study (JHS). Am Heart J 2009;158:209–216
17. Keku E, Rosamond W, Taylor HA, et al. Cardiovascular disease event classification in the Jackson Heart Study: methods and procedures. Ethn Dis 2005;15(4 Suppl. 6):S6-62-70
18. Gopal A, Nasir K, Liu ST, Flores FR, Chen L, Budoff MJ. Coronary calcium progression rates with a zero initial score by electron beam tomography. Int J Cardiol 2007;117:227–231